

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-954

ADMINISTRATIVE DOCUMENTS

NDA 20-954

OCT - 6 1998

Orphan Medical, Inc.
13911 Ridgedale Drive, Suite 475
Minnetonka, MN 55305

Attention: Dayton T. Reardon, Ph.D., RAC
Vice President of Regulatory Affairs

Dear Dr. Reardon:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Busulfex Injection (busulfan) sterile liquid, 60 mg ampoule

Therapeutic Classification: Priority (P)

Date of Application: August 3, 1998

Date of Receipt: August 4, 1998

Our Reference Number: 20-954

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on October 3, 1998 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be February 4, 1999.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

If you have any questions, contact Patrick Guinn, Project Manager, at (301) 827-1537.

Sincerely,

/s/

10-5-98

Dotti Pease
Chief, Project Management Staff
Division of Oncologic Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

NDA 20-954

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cc:

Archival NDA 20-954

HFD-150/Div. Files

HFD-150/RJustice

HFD-150/JBeitz

HFD-150/JJohnson

HFD-150/DGriebel

HFD-150/LZhou

HFD-150/NChidabaram

HFD-150/XChen

HFD-150/PAndrews

HFD-150/WMcGuinn

HFD-150/ARahman

HFD-150/SIbrahim

HFD-150/GChen

HFD-150/PGuinn

HFD-150/DPease

DISTRICT OFFICE

F/T: PGuinn/August 21, 1998/October 2, 1998
ACKNOWLEDGEMENT (AC)

EXCLUSIVITY SUMMARY FOR NDA # 20-954 SUPPL # _____

Trade Name Busulfex Injection Generic Name busulfan

Applicant Name Orphan Medical, Inc. HFD - 150
Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?
YES / X / NO / ___/

b) Is it an effectiveness supplement?

YES / ___/ NO / X /

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES / X / NO / ___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

Form OGD-011347 Revised 10/13/98

cc: Original NDA 20-954 HFD-150 Div. File
HFD-150/PGuinn

HFD-93 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /___/ NO / X /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety? No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO / X /

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO / X /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / X / NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 9-386

Myleran; Oral Tablet

NDA# _____

NDA# _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____

NDA# _____

NDA# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / X / NO / ___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / X / NO / ___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES / X / NO / ___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO / X /

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO / X /

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Two Phase 2 Trials: OMC-BUS-3 and OMC-BUS-4

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 OMC-BUS-3 YES /___/ NO / X /

Investigation #2 OMC-BUS-4 YES /___/ NO / X /

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 OMC-BUS-3 YES /___/ NO / X /

Investigation #2 OMC-BUS-4 YES /___/ NO / X /

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

OMC-BUS-3

OMC-BUS-4

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 OMC-BUS-3

IND # _____ YES / X / NO /___/ Explain: _____

Investigation #2 OMC-BUS-4

IND # _____ YES / X / ! NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/

NO / X /

If yes, explain: _____

/S/

1/21/99

Patrick Guinn
Project Manager

/date

/S/

M.D. 2/4/99

Robert L. Justice, M.D.
Acting Division Director

/date

cc: Original NDA 20-954
HFD-150/Division File
HFD-150/Patrick Guinn
HFD-93 Mary Ann Holovac

CONFIDENTIAL - Orphan Medical, Inc.

NDA 20-954 Busulfex™ (busulfan) Injection

SECTION 13.0 PATENT INFORMATION ON ANY PATENT WHICH CLAIMS THE DRUG

SECTION 13.0
PATENT INFORMATION ON ANY PATENT
WHICH CLAIMS THE DRUG

**SECTION 14**

July 22, 1998

PATENT CERTIFICATION

On behalf of Orphan Medical, Inc., I certify that the only U.S. patents that have not expired which claim the drug upon which investigations that are relied upon by the applicant for approval of its application were conducted or that claims an approved use for such drug and for which information is required to be filed under section 505(b) and (c) of the FFDCA are those for which Orphan Medical currently has exclusive licenses (Patent No.'s 5,430,057 and 5,559,148).

Other than the patents stated above, all other patents relevant to this NDA have expired. This information was confirmed by a patent search, from 1971 to present, on IBM's Patent Server site located on the world wide web site at <http://www.ibm.com./News/1997/01/1s970109.html>. The search term "busulfan" was used.

Dayton T. Reardan, Ph.D., RAC
Vice President of Regulatory Affairs



July 17, 1998

Food and Drug Administration

RE: NDA 20-954, Busulfex™ (busulfan) Injection

GENERIC DRUG ENFORCEMENT ACT OF 1992 CERTIFICATION

This information is submitted in accordance with Section 306(k)(1) of the Act [21 U.S.C. 335a (k)(1)].

I certify that Orphan Medical, Inc. did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [section 306(a) or (b)], in connection with this New Drug Application for Busulfex™ (busulfan) Injection.

Dayton T. Reardan, Ph.D., RAC
Vice President of Regulatory Affairs

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number: 20954 Trade Name: BUSULFEX (BUSULFAN) INJ 60MG AMPULE
Supplement Number: Generic Name: BUSULFAN
Supplement Type: Dosage Form: INJ

Regulatory Action: PN Proposed Indication: BUSULFEX (busulfan) Injection is indicated for use in combination with other chemotherapeutic agents and/or radiotherapy as a conditioning regimen prior to hematopoietic progenitor cell transplantation. Diseases in which patient benefit from this mode of therapy have been demonstrated include acute lymphocytic leukemia, acute non-lymphocytic leukemia, acute myeloid leukemia, chronic myeloid leukemia, non-Hodgkin's lymphoma, Hodgkin's lymphoma, multiple myeloma, myelodysplastic syndrome, breast cancer, ovarian cancer, and genetic diseases.

IS THERE PEDIATRIC CONTENT IN THIS SUBMISSION? NO

What are the INTENDED Pediatric Age Groups for this submission?

 NeoNates (0-30 Days) Children (25 Months-12 years)
 Infants (1-24 Months) Adolescents (13-16 Years)

Label Status
Formulation Status
Studies Needed
Study Status

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

Acceptable Indication: BUSULFEX (busulfan) Injection is indicated for use in combination with cyclophosphamide as a conditioning regimen prior to allogeneic hematopoietic progenitor cell transplantation for chronic myelogenous leukemia.

A pediatric trial was initiated and is ongoing under IND 46,232.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER,
PATRICK GUINN

Patrick Guinn
Signature

1/26/99
Date